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ORIGINAL PAPER

The role of sex on stability and change of depression symptom subtypes over 20 years: a latent transition analysis

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Abstract Prospective studies investigating the long-term stability of depression symptom subtypes are rare. Moreover, sex has received little attention as a predictor. This study aimed to investigate the role of sex on stability and transition patterns of depressive symptom subtypes over 20 years. The data were drawn from three follow-ups (1988, 1999, and 2008) of the longitudinal Zurich Study. Latent transition analyses were fitted to the data of 322 subjects, using depressive symptoms from the face-to-face interviews. The stable classes were characterized by psychosocial correlates. Three subtypes were identified: 'severe atypical,' 'severe typical,' and 'moderate.' While stability of the severe atypical and moderate subtype was relatively high and increased over time (70–71; 45–90 %), stability of the severe typical subtype was lower (45–48 %). Females had a higher risk of being in the severe atypical subtype and exhibited more transitions, particularly with respect to the severe typical subtype. In contrast, males displayed more stable subtypes. The stable severe atypical subtype was associated with comorbid eating disorders as well as psychosis syndromes, whereas the stable severe typical subtype was associated only with psychosis syndromes. Our results provide first evidence for the notion that long-term stability and transition patterns differ by sex and depression subtypes. This finding has received too little attention in previous research and should be considered in treatments.

Keywords Depression · Subtypes · Sex · Longitudinal studies · Epidemiology

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Introduction

Over the past decades, the recognition of the heterogeneity of major depressive disorder (MDD) resulted in the development of various depression subtype models. Research on subtypes of MDD is a promising approach toward a better understanding of etiology and type-specific treatments [10]. Three symptom-based subtypes are currently coded in the diagnostic and statistical manual of mental disorders (DSM-5) as the MDD specifiers: melancholic, atypical and psychotic depression [9]. In addition to the diagnostic classification system, there is a growing body of evidence from empirically derived symptom typologies based on cluster analysis and latent class analysis (LCA), confirming the existence of MDD subtypes [12, 18, 24, 28, 29, 42, 54, 55]. However, only few studies have investigated the longitudinal stability of MDD symptom subtypes, although the temporal stability displays an important aspect of the usefulness of subtype classifications [23]. Subsequently, these longitudinal findings of the melancholic, atypical, and psychotic subtype will be summarized:

Firstly, studies investigating the stability of the melancholic subtype have yielded rather inconsistent findings.

This may be attributable to the various definitions of melancholia and similar concepts such as endogenous depression and typical depression [10, 34]. Some studies found stability values between 30 % (community-based sample) [4] and 37 % (depressed inpatients) [23]. Other studies demonstrated a weak stability of the melancholic subtype in depressed in- and outpatients, leading to concerns regarding the validity of this MDD specifier [34, 60].

Secondly, the atypical depression demonstrated a moderate stability in the community-based longitudinal Zurich Study [7]. A further study showed that 90 % of depressive outpatients with reversed symptoms (hypersomnia, overeating, weight gain) at baseline manifested the same symptoms when they relapsed [38]. This stability was consistent with genetic epidemiology data of female twins, suggesting a genetic stability of the atypical subtype [24]. Yet in a small sample of atypical depressive patients, one-third with first onset of affective disorder was no longer atypical within a two-year follow-up [19, 27].

Thirdly, the stability of the psychotic subtype was confirmed by the finding that 92–95 % of psychotic depressive patients experienced another admission for an episode of depression with psychotic syndromes [13, 22]. Comparing the psychotic, agitated/retarded, and endogenous subtypes of depression, the psychotic subtype showed the highest diagnostic stability across multiple episodes. However, some authors [33] proposed that major depression with mood-congruent psychotic symptoms may not be a distinct diagnostic entity, but rather a more severe occurrence of depression.

However, complementary to stability issues, some research has provided support for the view that a shift from one depressive subtype to another might be common [4, 32]. Therefore, apart from the validation of depression-subtype stability, the investigation of transitions between the depression subtypes should be clarified in more detail. For examining the transitions between depression subtypes, the application of more suitable statistical methods is warranted than have been used in previous research.

A promising statistical approach for extracting homogeneous subgroups is LCA. The latent transition analysis (LTA) is the longitudinal extension of LCA, allowing for the estimation of stability and transition patterns among subtypes. To date, only one study has applied LTA to examine the transitions and stability of MDD subtypes longitudinally over a two-year follow-up period [30]. The highest stability over time was found for the moderate and the severe atypical classes. The probabilities for the severe typical class were slightly lower. The findings indicated relative stability across measurements and thereby confirmed the validity of these depressive subtypes. As Lamers et al. [30] noted, future research should investigate whether these patterns of stability and transitions are still identifiable over longer time periods.

In this context, previous longitudinal research has not taken sex into consideration as a potential predictor, despite the consistent empirical findings of higher rates of MDD in females [25, 57]. However, these findings have been explained by specific symptom-based depressive subtypes in females such as atypical, anxious, and somatic depression [7, 11, 15, 51, 52]. The inconsistent empirical evidence regarding sex differences in the course of MDD [47] could derive from the fact that MDD is a highly heterogeneous construct that should more appropriately be analyzed within the scope of symptom subtypes, their longitudinal stability as well as transition patterns.

Aims of the study

Therefore, the aims of the current study were: (1) to investigate the long-term stability and transitions of symptom-based depression subtypes over a period of 20 years, (2) to examine whether stability and transition patterns of these symptom subtypes meaningfully differ between males and females, and (3) to characterize resulting stable subtypes by relevant psychosocial correlates.

Methods

Study design and sample selection

The data were drawn from the prospective longitudinal Zurich Study [6]. The Zurich Study is based on an initial screening procedure. In 1978, a representative sample of young adults of the canton of Zurich in Switzerland was screened with the Symptom Checklist 90-R (SCL-90-R; [16]) and a socio-demographic questionnaire. This sample comprised 4,547 subjects (males = 2,201; females = 2,346), aged 19 years (males) and 20 years (females). Subsequently, a stratified sampling procedure was performed. This methodological approach was utilized to increase the proportion of subjects with a high risk of developing psychiatric syndromes/disorders in the sample. Based on the global severity index (GSI) of the SCL-90-R, two-thirds of high scorers (above the 85th ‰) and one-third of randomly assigned low scorers (below the 85th ‰) were selected, leading to a final subsample of 591 subjects (292 males; 299 females). Over 30 years, seven follow-up interviews were conducted in 1979, 1981, 1986, 1988, 1993, 1999, and 2008. The study was approved by the local ethics committee.

Of the original sample ($n = 591$), 335 (57 %) participated in the last follow-up 2008. The detailed participation

rates were as follows: 43 % in all seven interviews, 13 % in six interviews, 11 % in five interviews, 9 % in four interviews, 7 % in three interviews, 9 % in two interviews, and 9 % in one interview.

For the current study, the data of subjects who participated in any of the interviews 1988, 1999, and 2008 were included in the analyses. The restriction to these three follow-ups was made to keep the indicators identically over time and because the previous assessments differed with respect to the assessed depression symptoms. The follow-up 1993 was omitted in order to receive nearly equidistant time intervals.

The data of participants with missing data on all three follow-ups 1988, 1999, and 2008 were excluded from the analyses ($n = 269$). This led to a final subsample of 322 participants. The data of those subjects giving information at only one or two occasions, respectively, were considered in the LTA. In this context, the following patterns of missing data were observed: missing data on all items in *one* follow-up: 1988 $n = 44$ (13.7 %); 1999 $n = 23$ (7.1 %); 2008 $n = 37$ (11.5 %); and missing data on all items on *two* follow-ups: 1988 and 1999 $n = 31$ (9.6 %); 1999 and 2008 $n = 84$ (26.1 %); 1988 and 2008 $n = 55$ (17.1 %). According to Little's MCAR test ($\chi^2 = 452.751$, $df = 438$, $p = 0.303$), these missing values were missing completely at random (MCAR). We decided not to impute the data of complete follow-ups to maintain the data quality as high as possible and to improve the estimation of the time-specific parameters. However, 17 participants (5.3 %) had missing values on one item and in one case on two items in 1999, despite they participated in the interview. The Little's MCAR test ($\chi^2 = 56.085$, $df = 59$, $p = 0.584$) revealed again that these missing values were MCAR. Based on the subjects' complete items of 1999, the missing values were replaced by values derived by multiple imputation, which relies on Bayesian analysis [45, 46] in Mplus.

After performing the LTA, we selected subjects remaining in the same class over the three time points 1988, 1999, and 2008 in order to characterize these resulting stable subtypes. This led to a subsample of 174 subjects.

Measures

The Structured Psychopathological Interview and Rating of Social Consequences of Psychic Disturbances for Epidemiology (SPIKE) is a comprehensive face-to-face interview assessing a number of somatic and psychopathological syndromes/disorders for the previous 12 months [3]. The SPIKE was administered in the participants' homes by clinical psychologists or psychiatrists trained intensively in the use of the instrument [2]. Validity and reliability have been established particularly for depression and anxiety. The inter-rater reliability of the SPIKE was high, with kappas of 0.90 for the syndromal diagnosis. Moreover, the SPIKE was found to have high sensitivity and modest specificity for detecting depression at the diagnostic level and a good sensitivity with respect to the subthreshold level [6].

For the current study, algorithms of psychiatric diagnoses were used according to the respective version of DSM-III, DSM-III-R, DSM-IV, and ICD-10 [6, 8, 58]. Furthermore, the presence of the two psychosis syndromes psychoticism and paranoia was computed using the schizophrenia nuclear symptoms (SNS) and schizotypal signs (STS) subscales [44] derived from the SCL-90-R [17].

Only subjects affirming either the first or second filter question of the section depression were included in the data analyses. We considered 15 binary-coded depressive symptoms ('Symptom existent during the past 12 months?' 0 = no; 1 = yes) representing the nine DSM-IV 'A' criteria for major depression. Additionally, we disaggregated appetite loss/gain, weight loss/gain, insomnia/hypersomnia, and psychomotor agitation/retardation, due to the fact that these criteria are antipodal, and moreover, we included the atypical feature 'irritability/anger.' These symptoms were assessed for the time frame of the last 12 months without considering criteria of frequency and durability.

Statistical analysis

Latent transition analysis (LTA) is a longitudinal mixture model that accounts for individual transitions between categorical latent classes over time [37, 39]. Based on the interindividual response pattern to manifest items, homogeneous subgroups (latent classes) of individuals are extracted. At each time of measurement, an LCA is postulated, and stage-sequential development is summarized in transition probability of latent classes over two serial times. When covariates are considered, transition probabilities are conditioned not only by the previous time point, but also as a function of the value of the covariate [39]. The resultant measurement parameters are the transition probabilities from time 1 to 2, time 2 to 3, etc., the class membership probability, and the conditional item probabilities, estimated for each class at the several time points [14, 39].

Commonly used statistical fit indices for model comparisons are the Bayesian information criterion (BIC; [49]), the sample-size-adjusted BIC (ABIC; [50]), and the entropy measure (ranging from 0 to 1). Low BIC and ABIC values and a high entropy index indicate a better model fit. The final selection is commonly guided by the combination of the statistical fit indices with the theoretical interpretability of a given class solution [35].

First, exploratory cross-sectional LCA was performed for the years 1988, 1999, and 2008. To determine the optimal number of latent classes, one to five latent class

models were fitted to the data. These models were compared by BIC, ABIC, and entropy. After performing the unconditional LCA, the covariate sex was included at each time point. Second, we explored whether full (all conditional item probabilities are equal) or partial (part of the conditional item probabilities are equal) measurement invariance should be assumed across the time points [39]. This was performed using deviance statistic [53]. Given that the chi-square value of partial invariance and full non-invariance was not significant, partial measurement invariance was assumed for the time points 1988, 1999, and 2008. Finally, longitudinal LTA was fitted to the data for the three time points 1988 to 1999 to 2008 (age 29–50). Latent transition probabilities were first computed in an unconditional model without a covariate and subsequently in a conditional model including the covariate sex (providing an output separately for each covariate group).

Latent class analysis (LCA), LTA, and multiple imputation were carried out using Mplus, version 7, for Macintosh [37]. In each analysis, the number of random starts was set up to 5,000, using the 500 best solutions in the final calculation. Chi-square tests, Fisher's exact tests, Kruskal–Wallis tests, and multinomial logistic regressions (odds ratios [OR] with 95 % confidence intervals [CI]) were computed using SPSS statistics, version 20, for Macintosh (SPSS Inc., USA).

Results

Model selection on the basis of latent class analysis

Five exploratory LCA models were fitted to each of the three time points 1988 ($n = 192$), 1999 ($n = 184$), and 2008 ($n = 146$). Table 1 compares the resulting model fit indices, beginning with the most parsimonious one-class model through to a five-class model. The BIC and ABIC indicated that the three- or four-class solution provides the best fit to the data. After a comparison of the plotted estimated symptom probabilities, the three-class LCA model was chosen, as more classes produced only further moderate classes of questionable meaning.

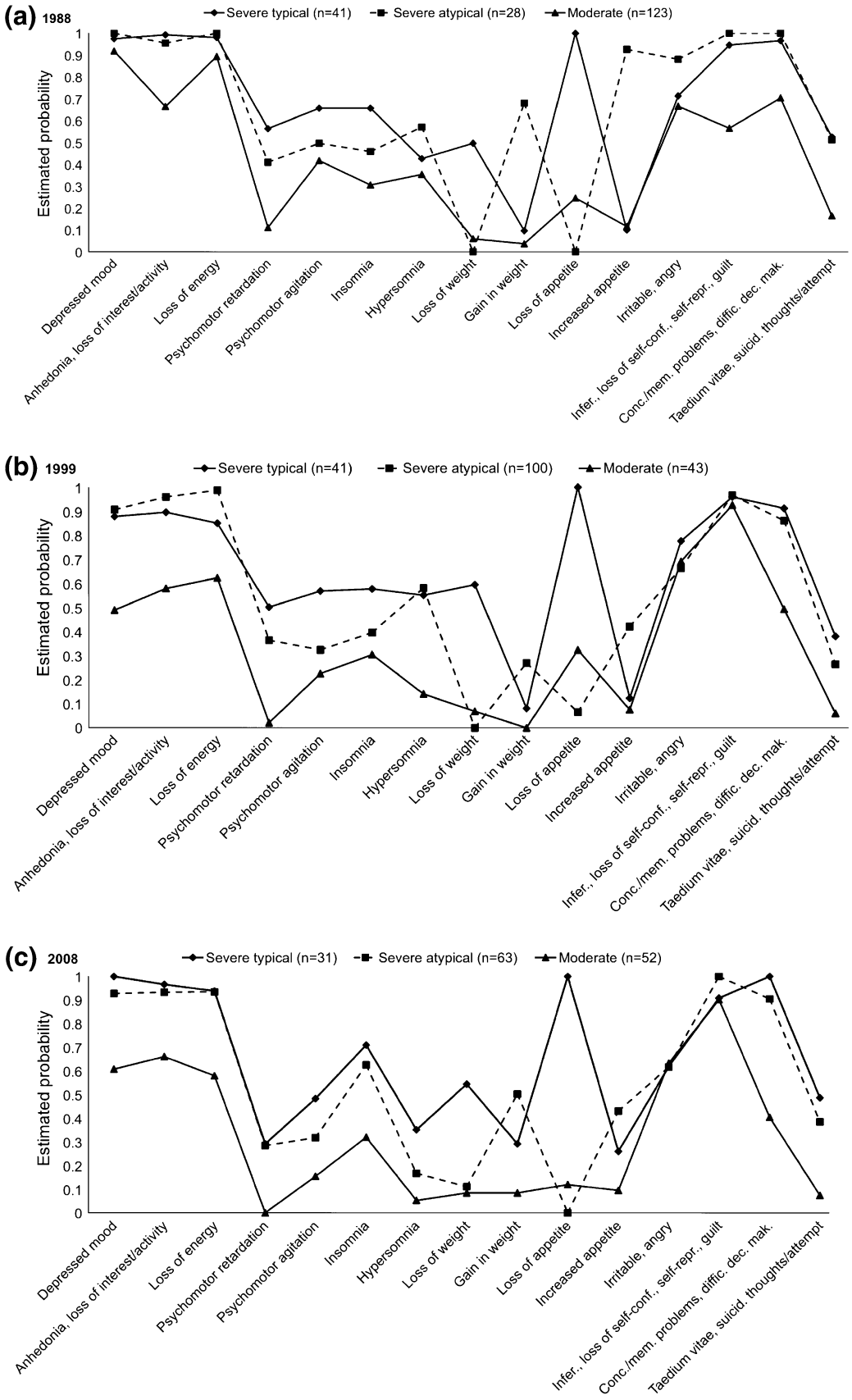
The plotted estimated symptom probabilities showed that class one was characterized by a high probability for typical depressive symptoms such as loss of weight and appetite. Therefore, this class was labeled 'severe typical.' Subjects of class two endorsed symptoms such as weight gain and increased appetite. Because of its high probabilities for an atypical symptom pattern, this class was labeled 'severe atypical.' Finally, the third class exhibited less-pronounced symptom probabilities and was labeled 'moderate.' The inclusion of the covariate sex at each time point

Fig. 1 Symptom probability plots across the three latent classes with the covariate sex at (**a**) aggregated items: feelings of inferiority, loss of self-confidence, self-reproaches, excessive guilt; concentration/memory problems, difficulties in decision making; disaggregated items: appetite loss/gain, weight loss/gain; insomnia/hypersomnia; psychomotor agitation/retardation 1988. (**b**) Aggregated items: anhedonia, loss of interest and activity; feelings of inferiority, loss of self-confidence, self-reproaches, excessive guilt; concentration/memory problems, difficulties in decision making; tiredness of life (taedium vitae), suicidal ideation, suicidal attempt; disaggregated items: appetite loss/gain, weight loss/gain; insomnia/hypersomnia; psychomotor agitation/retardation. 1999, and (**c**) aggregated items: anhedonia, loss of interest and activity; feelings of inferiority, loss of self-confidence, self-reproaches, excessive guilt; concentration/memory problems, difficulties in decision making; tiredness of life (taedium vitae), suicidal ideation, suicidal attempt; disaggregated items: appetite loss/gain, weight loss/gain; insomnia/hypersomnia; psychomotor agitation/retardation 2008

Table 1 Model fit indices derived from latent class analysis with classing ranging from 1 to 5 of the subsamples of subjects with depressive symptoms: 1988, 1999, and 2008

Fit statistics	1-class	2-class	3-class	4-class	5-class
1988					
BIC	3,129.496	3,072.124	3,071.092	3,077.914	3,130.418
ABIC	3,081.981	2,973.925	2,922.210	2,878.350	2,880.171
Entropy	N/A	0.674	0.781	0.865	0.896
1999					
BIC	2,982.627	2,952.934	2,946.428	2,978.587	3,026.775
ABIC	2,935.118	2,854.749	2,797.567	2,779.050	2,776.563
Entropy	N/A	0.686	0.794	0.855	0.934
2008					
BIC	2,384.924	2,331.032	2,372.208	2,420.004	2,470.751
ABIC	2,337.457	2,232.935	2,223.479	2,220.644	2,220.759
Entropy	N/A	0.748	0.842	0.857	0.882

BIC Bayesian information criterion, *ABIC* sample-size-adjusted Bayesian information criterion


(a) 1988
Severe typical (n=41)
Severe atypical (n=28)
Moderate (n=123)
Estimated probability
Depressed mood
Anhedonia, loss of interest/activity
Loss of energy
Psychomotor retardation
Psychomotor agitation
Insomnia
Hypersomnia
Loss of weight
Gain in weight
Loss of appetite
Increased appetite
Irritable, angry
Infer., loss of self-conf., self-repr., guilt
Conc./mem. problems, diffic. dec. mak.
Taedium vitae, suicid. thoughts/attempt
(b) 1999
Severe typical (n=41)
Severe atypical (n=100)
Moderate (n=43)
Estimated probability
(c) 2008
Severe typical (n=31)
Severe atypical (n=63)
Moderate (n=52)
Estimated probability

indicated significant sex differences with respect to the latent classes with a higher proportion of females in the severe atypical class. Figure 1 depicts the plots of the estimated symptom probabilities derived from the LCA after inclusion of the covariate sex for each time point.

Latent transition analysis

The estimated transition and stability probabilities derived from the LTA are presented in Table 2. Compared to the unconditional model, the stability coefficients of the conditional model including the covariate sex were quite similar. In the conditional model, class stability was higher in the moderate and severe atypical class than in the severe typical class. Remarkably, the stability of the moderate class even increased in the second time period above 90 %, while the severe typical and severe atypical classes nearly remained unchanged.

When individuals transitioned to a different class over time, they predominantly changed from the severe typical to the severe atypical and moderate classes. However, noteworthy transitions also occurred from the severe atypical to the severe typical class, whereas moves from the moderate to the severe atypical class declined over time.

Sex ratios were computed for the LTA classes of the conditional model (not tabulated). In 1988, multinomial logistic regressions revealed a significantly higher risk for females belonging to the severe atypical latent class (OR 2.84, CI 1.18–6.83) (typical class: $n = 33$ males, $n = 22$ females; atypical class: $n = 7$ males, $n = 25$ females; moderate class: $n = 105$ males, $n = 132$ females). In 1999, the odds ratio associated with the severe atypical class (OR 2.35, CI 1.43–3.88) was significantly higher for females (typical class: $n = 31$ males, $n = 21$ females; atypical class: $n = 39$ males, $n = 88$ females; moderate class: $n = 73$ males, $n = 70$ females). In 2008, there was still a significantly higher risk for females being in the severe atypical class (OR 1.81, CI 1.10–2.96) (typical class: $n = 27$ males, $n = 22$ females; atypical class: $n = 41$ males, $n = 78$ females; moderate class: $n = 75$ males, $n = 79$ females).

The latent transition probabilities of the conditional model revealed meaningful sex differences (Table 2). Males exhibited a higher stability within the latent classes, and moreover, stability substantially increased over time. Interestingly, transitions were more prominent in females for both time intervals, particularly regarding movements from the severe typical to the severe atypical class and vice versa. In contrast, no male transitioned from the atypical class to the typical class. In addition, females revealed changes from the severe typical class into the moderate class.

Psychosocial correlates of stable depression subtypes

Longitudinally stable subtypes might be more reliable than subtypes derived cross-sectionally [30]. Consequently, for the next analysis, we selected persons exhibiting the same class membership over the three time points 1988, 1999, and 2008 and excluded subjects transitioning between the three subtypes at least once. This led to a subsample of 174 persons [severe atypical class: $n = 19$ (10.9 %); severe typical class: $n = 26$ (14.9 %); moderate class: $n = 129$ (74.1 %)]. In terms of demographics, the latent stable classes differed significantly by sex. The severe atypical subtype comprised significantly more females, whereas the severe typical subtype included significantly more males.

Table 2 Estimated transition and stability (bold) probabilities across the time points 1988 to 1999 to 2008 for the unconditional model, the conditional model including the covariate sex and separately for males and females, $n = 322$

1988	Unconditional model (overall)			Conditional model (overall)			Conditional model (males)			Conditional model (females)		
	1999			1999			1999			1999		
	Severe typical	Severe atypical	Moderate	Severe typical	Severe atypical	Moderate	Severe typical	Severe atypical	Moderate	Severe typical	Severe atypical	Moderate
Severe typical	**0.370**	0.443	0.187	**0.446**	0.354	0.200	**0.543**	0.122	0.334	**0.359**	0.562	0.079
Severe atypical	0.332	**0.607**	0.061	0.149	**0.704**	0.148	0.000	**0.545**	0.455	0.192	**0.750**	0.059
Moderate	0.093	0.412	**0.495**	0.123	0.426	**0.451**	0.089	0.483	**0.428**	0.157	0.370	**0.473**
1999	2008			2008			2008			2008		
Severe typical	**0.367**	0.409	0.224	**0.481**	0.292	0.227	**0.666**	0.334	0.000	**0.344**	0.261	0.395
Severe atypical	0.238	**0.672**	0.089	0.198	**0.708**	0.094	0.000	**0.765**	0.235	0.324	**0.671**	0.005
Moderate	0.000	0.117	**0.883**	0.024	0.074	**0.902**	0.046	0.000	**0.954**	0.000	0.157	**0.843**

The sex proportion of the moderate class was almost in balance. Further psychosocial characteristics of the stable subgroups are presented in Table 3.

Table 4 displays odds ratios and confidence intervals (95 %) from multinomial logistic regressions, characterizing the comorbidity patterns of stable classes. The moderate class is treated as reference class. Bulimia/binge eating and psychosis syndromes were significantly associated with an increased risk of membership in the severe atypical class in comparison with the moderate class. On the other hand, the severe typical class differed from the moderate class solely with respect to psychosis syndromes. Additional multinomial logistic regression analyses contrasting the severe typical subtype versus the severe atypical subtype showed a significantly ($p < 0.01$) lower risk of bulimia/binge eating (OR 0.08, CI 0.01–0.46) in the severe typical class (not tabulated). While childhood/adolescence adversity was linked to the severe atypical class, unemployment was a critical life event characterizing the severe typical class.

Discussion

This study aimed at analyzing the role of sex on stability and transition patterns of empirically derived depression subtypes in a prospective epidemiologic sample over 20 years. To the best of our knowledge, this is the first latent transition analysis study examining such a long time period. We identified three depression subtypes—'severe atypical,' 'severe typical,' and 'moderate'—with relevant sex-related differences in the long-term stability and the transition patterns. Between 29 and 50 years of age, stability of depression subtypes strongly increased in males. In contrast, females displayed more transitions between the subtypes. The subtype with the highest instability and the most transitions was the severe typical subtype, and especially, changes to the severe atypical subtype and vice versa were prominent.

Latent transition analysis: from cross-sectional to longitudinal evidence

The empirical identification of the subtypes 'severe atypical' and 'severe typical' is in line with the MDD specifiers of DSM-IV and with the results of earlier subtyping studies [24, 29, 30, 54, 55]. The fact that we could distinguish a moderate subtype from the two severe subtypes is also consistent with previous reports, suggesting that both symptom patterns and severity meaningfully contribute to explaining the heterogeneity of MDD [28]. However, our analyses were longitudinal and therefore provide evidence regarding the long-term validity of these psychopathological constructs. In the following, we will focus on longitudinal studies investigating depression subtypes.

In line with previous findings of atypical depression being characterized by longer episodes and higher chronicity than other subtypes [7], the current study found a high stability of the severe atypical subtype over time. The only previous study applying LTA to symptom-based depression subtypes was conducted by Lamers et al. [30]. They found similar stability values for the atypical subtype (79 %) and moderate subtype (78 %), but obtained much higher stability coefficients for the severe typical subtype (71 %). However, consistent with the present study, two previous studies found stability coefficients for the melancholic (typical) subtype of 37 % [23] and 30 % [4], respectively. One of the two studies, conducted by Angst et al. [4], and the current study were based on the same sample, but differed with regard to procedures and methodology. Angst et al. computed subtypes for all six interviews, while we restricted the number of follow-ups to three interviews. Methodologically, our subtypes were estimated by a data-derived technique, while Angst and colleagues defined the subtypes by DSM-IV specifiers. More precisely, our methodological approach was person-centered (focus on relationships between individuals; goal: to group individuals into homogeneous categories); by contrast, Angst et al. had a variable-centered approach (focus on relationships between variables; goal: to predict outcomes) [36]. In contrast to our three derived subtypes, Angst et al.'s study additionally investigated a combined group manifesting melancholia or atypical depression and a subgroup with an unspecified syndrome.

The transition patterns we found in our study were similar to those earlier observed by Lamers et al. [30]. The membership changes occurred from the moderate to the severe atypical, from the severe atypical to the severe typical, and from the severe typical to the moderate subtypes. Minor discrepancies in our findings (moves from the severe typical to the severe atypical subtype) might be explained by dissimilar time frames and further methodological differences in Lamers et al.'s [30] study such as sample characteristics (no pure community sample), a broader age range (18–65 years), differing eligibility criteria (MDD diagnosis at both baseline and follow-up), and the exclusion of certain primary clinical diagnoses, such as psychotic disorder, bipolar disorder and addiction disorder.

Sex-related differences: (a) instability of depression subtypes in females

As mentioned above, our results generally indicated that females' phenotype of depression longitudinally exhibited a heterogeneous presentation, with syndromes changing

Table 3 Psychosocial characteristics for the stable classes ($n = 174$) derived from latent transition analysis including the covariate sex

	Latent classes			
	Severe typical $n = 26$ % (n)	Severe atypical $n = 19$ % (n)	Moderate $n = 129$ % (n)	χ^2/F test Overall p value (two-tailed)
Sex				$p < 0.001^{I,II,III}$
Female	11.5 (3)	94.7 (18)	50.4 (65)	
Male	88.5 (23)	5.3 (1)	49.6 (64)	
Education[1]				$p = 0.437$
Secondary general school	43.5 (10)	27.8 (5)	35.8 (44)	
Intermediate secondary school	43.5 (10)	33.3 (6)	35.8 (44)	
Grammar school	13.0 (3)	38.9 (7)	28.5 (35)	
Familiar depression[2]	26.9 (7)	16.7 (3)	13.6 (17)	$p = 0.228$
Comorbid psychiatric disorder/syndrome (lifetime)				
MDD[b]	26.9 (7)	15.8 (3)	17.8 (23)	$p = 0.500$
MDD/DYST/RBD/MIND[b]	92.3 (24)	84.2 (16)	71.3 (92)	$p < 0.05^{III}$
MDD and manic symptoms[c]	38.5 (10)	47.4 (9)	21.7 (28)	$p < 0.05^{II}$
Neurasthenia[d]	23.1 (6)	31.6 (6)	14.7 (19)	$p = 0.140$
GAD[a]	42.3 (11)	57.9 (11)	21.7 (28)	$p < 0.01^{II,III}$
Simple phobia[b]	15.4 (4)	26.3 (5)	14.0 (18)	$p = 0.321$
Agoraphobia[b]	15.4 (4)	31.6 (6)	8.5 (11)	$p < 0.05^{II}$
Social phobia[b]	26.9 (7)	42.1 (8)	15.5 (20)	$p < 0.05^{II}$
OCD[b]	11.5 (3)	10.5 (2)	5.4 (7)	$p = 0.311$
Panic disorder[a]	15.4 (4)	10.5 (2)	8.5 (11)	$p = 0.480$
Psychoticism syndrome[e]	31.6 (6)	16.7 (3)	1.1 (1)	$p < 0.001^{II,III}$
Paranoia syndrome[e]	26.3 (5)	38.9 (7)	6.5 (6)	$p < 0.001^{II,III}$
Bulimia[b,c]	3.8 (1)	15.8 (3)	1.6 (2)	$p < 0.05^{I,II}$
Binge eating (at least symptoms)[b,c]	8.0 (2)	37.5 (6)	9.4 (12)	$p < 0.01^{I,II}$
Tobacco dependence[a]	73.1 (19)	47.4 (9)	52.7 (68)	$p = 0.129$
Alcohol abuse/dependence[c]	46.2 (12)	52.6 (10)	30.2 (39)	$p = 0.072$
Substance abuse/dependence[c]	30.8 (8)	10.5 (2)	15.5 (20)	$p = 0.151$
	Mean rank (n)	Mean rank (n)	Mean rank (n)	Kruskal–Wallis test p value
Childhood/adolescence adversity[3]				
Family/conduct problems (total score)	78.0 (24)	98.5 (19)	70.1 (106)	$p < 0.05$
Critical life events[4]				
New job	70.2 (26)	97.1 (19)	88.3 (127)	$p = 0.130$
Unemployment	80.6 (26)	85.7 (19)	87.8 (127)	$p = 0.753$
To move house	72.0 (26)	85.5 (19)	89.6 (127)	$p = 0.223$
Financial difficulties	72.4 (25)	76.7 (19)	80.8 (113)	$p = 0.170$

MDD major depression disorder, *DYST* dysthymia, *RBD* recurrent brief depression, *MIND* minor depression, *GAD* generalized anxiety disorder, *OCD* obsessive-compulsive disorder

[1] $n = 10$ missing data

[2] Mother, father, brother/sister, including several family members $n = 5$ missing data

[3] Derived from tetrachoric factor analysis; $n = 25$ missing data

[4] Sum of critical life events (1988, 1999, 2008); $n = 1$–17 missing data

[a] DSM-III; [b] DSM-III-R; [c] DSM-IV; [d] ICD-10; [e] schizophrenia nuclear symptoms (SNS) and schizotypal signs (STS) subscales (Rössler et al. [44])

[I] Class 1 significantly differs from class 2; [II] Class 1 significantly differs from class 3; [III] Class 2 significantly differs from class 3

Table 4 Odds ratios and confidence intervals (95 %) from multivariate multinomial logistic regressions for the stable classes ($n = 174$) derived from latent transition analysis including the covariate sex (severe atypical class: $n = 1$ male, $n = 18$ females; severe typical class: $n = 23$ males, $n = 3$ females; moderate class: $n = 64$ males, $n = 65$ females)

	Latent classes Severe atypical vs. moderate (ref.)	Severe typical vs. moderate (ref.)
Education		
Secondary general school	0.54 (0.10–2.99)	2.63 (0.45–15.24)
Intermediate secondary school	0.42 (0.07–2.35)	2.44 (0.45–13.14)
Grammar school (referent)		
Familiar depression	1.44 (0.20–10.25)	0.30 (0.06–1.42)
Comorbid psychiatric disorder/syndrome (lifetime)		
Any affective disorder	0.82 (0.10–7.05)	1.45 (0.22–9.44)
Any anxiety disorder	1.17 (0.28–4.88)	2.22 (0.58–8.48)
Alcohol/drug disorder	1.41 (0.30–6.54)	1.08 (0.26–4.43)
Bulimia/binge eating	13.00 (2.40–70.53)**	1.22 (0.12–12.76)
Psychosis syndromes	13.78 (2.31–82.31)**	7.38 (1.64–33.23)**
Childhood/adolescence adversity		
Family/conduct problems (total score	1.32 (1.03–1.70)*	0.93 (0.73–1.19)
Critical life events		
New job	2.78 (0.80–9.60)	0.41 (0.16–1.06)
Unemployment	0.52 (0.09–3.14)	4.01 (1.07–14.95)*
To move house	0.41 (0.10–1.73)	0.36 (0.13–1.04)
Financial difficulties	1.26 (0.09–18.60)	0.26 (0.04–1.92)

Affective disorders: MDD, dysthymia, recurrent brief depression, minor depression, MDD with manic symptoms, neurasthenia; anxiety disorders: agoraphobia, obsessive-compulsive disorder, simple phobia, panic disorder, generalized anxiety disorder, social phobia; alcohol/drug disorders: alcohol abuse/dependence, substance abuse/dependence, tobacco dependence; psychosis syndromes: psychoticism, paranoia

For detailed information with respect to the variables used, see Table 3

Ref reference

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

more frequently and a lower stability within distinct symptomatic subtypes of depression. Notably, our results indicated that the questionable validity of the typical subtype [34] concerned especially females. On the basis of our results, we speculate that the more frequent transitions across the three depressive subtypes in women may be explained by hormonal fluctuations of the perimenstrual phase. In support of this notion, results of prospective epidemiologic surveys have revealed a clear cycle-dependent vulnerability for affective symptoms [26, 43].

In our analyses, the transitions from the severe typical to the atypical class and vice versa were particularly pronounced. Recently, a biological link between changing profiles of typical (melancholic) and atypical subtypes has been proposed as a 'switch hypothesis,' considering specific regulations of the hypothalamic–pituitary–adrenal (HPA) axis [40], which, in turn, is influenced by ovarian hormones [59]. Consideration of bipolar disorders I/II might provide further explanation for instability of depressive syndromes in females. Although there are no sex differences in lifetime prevalence of bipolar disorders, the phenomenology differs with respect to a higher number of depressive episodes and of rapid-cycling patterns in bipolar females, as opposed to more manic episodes in bipolar males [26, 31, 56].

Sex-related differences: (b) sex-related stable depression subtypes

The stable severe atypical, severe typical, and moderate subtypes demonstrated considerable sex differences. As expected, the stable severe atypical subtype was significantly related to female sex compared to both the moderate and the severe typical subtypes. These results are in line with the finding that the sex ratio consistently found in depression might be attributed to atypical features [7, 11, 20]. On the contrary, the stable severe typical subtype showed a higher proportion of males. Our findings are in accordance with a previous analysis of Zurich Study data, in which the typical subtype (melancholia) occurred somewhat more frequently among males [4].

Sex-related differences: (c) stability of depression subtypes in males

In males, the long-term stability of depression subtypes was more pronounced in comparison with females. Whereas the overall prevalence of MDD is higher for females [25, 57], for the group of males manifesting stable severe subtypes, the course is chronic, at least over the examined time span of 20 years. Considering the generally higher suicide rates of males [21], the group of males of the stable severe subtypes deserves particular attention in research and practice.

Psychosocial correlates of stable depression subtypes

Above and beyond the sex-related differences, the stable depression subtypes differed with respect to comorbid disorders, childhood/adolescence adversity, and critical life events. While childhood/adolescence adversity was more pronounced in the severe atypical subtype, unemployment was significantly associated with the severe typical class. However, as Baumeister and Parker [10] noted in their recent meta-review, previous psychosocial correlates,

which have been proposed to characterize melancholic (typical) depression, revealed inconclusive results. For atypical depression, they were restricted to rejection sensitivity [10]. The stable severe subtypes differed from the moderate subtype with respect to the following comorbid lifetime disorders: (1) The severe atypical subtype was characterized by a significantly higher risk of bulimia/binge eating and psychosis syndromes. The association between eating patterns and atypical depression in females [7] has been explained by a common heredity [for an overview see 20]. (2) The severe typical subtype only showed a higher risk of comorbid psychosis syndromes. Thus, in our data, the occurrence of psychosis was a matter of severity.

Moreover, there is an ongoing debate in psychopathology research whether depression is best modeled using a unitarian or a binary model [41]. In the present study, the two stable severe subtypes seem to present symptom clusters, suggesting an underlying continuum, concordant with the unitarian concept of psychiatric disorders proposing a continuum from affective to schizophrenic syndromes [for an overview see 1]. This assumption is in accordance with our classificatory analyses, as Parkers [41] claims a paradigm shift in classifying depressive disorders considering both dimensional and categorical models ('mix and match' modeling paradigm). Hence, in contrast to the current DSM-IV specifiers, we did not detect the psychotic subtype as a distinct subgroup. This supports the view that psychotic depression is rather a more severe subtype of depression [33].

The comparison of the stable severe atypical with the severe typical subtype showed significant differences regarding the comorbid disorder bulimia/binge eating. The associations of atypical depression with comorbid panic disorder, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, and bipolar II disorders found in previous research [5, 7, 11] could not be replicated here multivariately. How can the discrepant co-occurrence of comorbid disorders found in previous studies and in our study be explained? Levitan et al. [32] identified a group of depressed subjects fluctuating between typical and atypical episodes, which manifested high rates of comorbid disorders. The authors believe that the inclusion of this subgroup in the investigation of atypical depressed has led to an overestimation of comorbid disorders in previous research [32]. Consequently, we can support the view of Levitan et al. [32]. The differentiation between the stable atypical and typical subtype seems to be restricted, if at all, to eating syndromes such as bulimia [32]/binge eating.

Taken together, we found more similarities than discrepancies between the two severe depression subtypes regarding the profile of comorbid disorders. This finding has also been reported by Angst et al. [4]. In the current analyses, however, the strongest delineations between the severe atypical and severe typical subtypes emerged from the symptom profiles and the factor sex.

Limitations and strengths

The following limitations of our study need to be acknowledged. First, the data contained some missing values regarding complete follow-ups. Yet, when we replicated the analyses in an exploratory approach with multiple imputation, the main results did not change. Second, the single mental syndromes/disorders were aggregated into broad categories in the multivariate logistic regression analyses due to the small cell sizes and in order to gain a tightly structured overview of the comorbidity profiles of the stable latent classes. Therefore, the variance of these single disorders, such as GAD, was attenuated. Third, the data did not contain any information about diagnosed personality disorders, although they were associated with atypical depression [48]. It has been suggested that this association could be particularly high for individuals who oscillate between typical and atypical features [32]. Fourth, we restricted the LTA indicators to the section depression for statistical reasons of parsimony, although somatic and anxious depression phenotypes have also been considered as female specific [15, 52]. Fifth, it could be argued that we should have limited our analyses to subjects meeting the criteria of an MDD. We intentionally remained on the depressive symptom level in order to account for the significance of subthreshold symptomatology, as already done in a recent latent analysis approach [12]. Furthermore, we did not exclude subjects with bipolar disorders or psychosis to allow for the investigation of the whole spectrum ranging from affective syndromes to psychosis syndromes. Sixth, we focused on symptom-based depressive subtypes and omitted other depressive subtyping models such as time of onset-based subtypes containing early- and late-onset depression and seasonal affective disorder [10]. Seventh, we cannot exclude the possibility that the observed changes in disorder characteristics are the result of differing raters.

Notwithstanding these limitations, this is the first study utilizing latent transition models to investigate the role of sex on stability and transition patterns over a time period of 20 years. The positive news for the persons providing data is that we could observe some transitions from severe subtypes into the moderate group, which is hopefully associated with a decreasing disease burden. On the other hand, the considerable longitudinal stability of atypical depression strongly suggests the provision of type-specific treatments [10]. The development of such type-specific treatments will be of particular importance to adequately address sex-specific requirements.

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Conflict of interest None.

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